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Individual differences in smoking reward from de-nicotinized cigarettes

Lisa H. Brauer, Frederique M. Behm, James D. Lane, Eric C. Westman, Christine Perkins, Jed E. Rose

Most studies of cigarette smoking and smoking cessation have focused on the psychopharmacological effects of nicotine; relatively few have explored the role of sensory aspects of cigarette smoke. Sensory aspects of cigarette smoke play a role in the maintenance of smoking behavior, and may be particularly important for certain smokers. This paper presents the results of a pooled analysis of nine studies conducted in our laboratory, in order to explore the influence of demographic and smoking-related variables on ratings of de-nicotinized as compared to nicotine-containing cigarettes. A major finding of this analysis is that ratings of smoking derived from de-nicotinized, but not nicotine-containing, cigarettes appear to vary with level of tobacco dependence, suggesting that sensory factors may be more important to highly dependent, as compared to less-dependent, smokers. The implications of these findings for smoking cessation treatment and for future research are discussed.

Introduction

Laboratory and clinical studies of smoking behavior have typically focused on the role of nicotine in the maintenance of smoking and the potential utility of nicotine replacement strategies for smoking cessation, respectively. The emphasis on nicotine, as opposed to other constituents of tobacco, has obvious merit given the large body of evidence that the reinforcing effects of nicotine play a significant role in smoking (reviewed in USDHHS, 1988). However, there is a growing body of evidence suggesting that other aspects of cigarette smoke, namely the sensory effects, also contribute to the maintenance of smoking. To date, sensory aspects of smoking have received relatively little attention in the basic and clinical literature. Understanding the role of sensory and other non-psychopharmacological effects of smoking is important for several reasons. First, clinical studies have demonstrated only modest efficacy of nicotine replacement strategies for smoking cessation (Fagerström, 1988; Hughes & Glaser, 1993; Palmer, Buckley, & Faulds, 1992; Sutherland *et al.*, 1992), and it is important to assess whether the addition of a sensory replacement component could enhance quit rates. Second, sensory replacement may prove useful in particular smokers for whom other forms of smoking cessation treatment have not been effective. Finally, assessing the role of non-psychoactive components of cigarette smoke would aid in our understanding of the relationship between primary and secondary reinforcers (e.g., Rose & Levin, 1991) in cigarette smoking, and in drug addiction generally.

Few studies have directly explored sensory aspects of smoking; however, studies have consistently demonstrated the importance of these factors to the maintenance of smoking. For example, Rose and colleagues have shown in a series of studies that pharmacological blockade of the afferent pathways mediating smoking-

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induced airway sensations significantly reduces smoking satisfaction (Rose, 1988; Rose, Tashkin, Ertle, Zinser, & Lafer, 1985; Rose, Zinser, Tashkin, Newcomb, & Ertle, 1984). These investigators, as well as others, have also shown that replacing the sensory component of smoking with substances including ascorbic and citric acids, capsaicin, black pepper, or refined smoke aerosol significantly reduces craving for cigarettes as well as rates of *ad lib* smoking (Behm & Rose, 1994; Levin, Behm, Carnahan, LeClair, Shipley, & Rose, 1993; Perkins, Grobe, Stiller, Fonte, & Goettler, 1992; Rose & Behm 1987; Rose & Behm 1994; Rose & Behm 1995; Westman, Behm, & Rose, 1995). Finally, it has been shown that treatments that re-create the mouth, throat, and airway sensations of smoking enhance the efficacy of the nicotine patch in smokers attempting to quit (Westman, Behm, & Rose, 1995). When taken together, these findings clearly demonstrate that there is more to smoking than the psychopharmacological effects of nicotine.

One reason for the relative paucity of studies on the sensory effects of smoking is that until relatively recently, there have been few methods available for experimentally separating the pharmacological and sensory components of cigarettes in order to assess their relative roles in maintaining smoking. Methods that were previously used were fraught with limitations related to differences between the experimental manipulation and commercially available cigarettes in the pattern and pharmacokinetics of nicotine administration, the palatability and/or sensory effects of experimental, as compared to commercially available, cigarettes, and the inability to vary nicotine and tar independently.

Recently, cigarettes low in nicotine but with standard levels of tar have become available for directly exploring the role of nicotine and sensory factors in smoking: the Next® cigarette, developed by Philip Morris, Inc.; the University of Kentucky cigarettes; and low nicotine cigarettes by Ultratech Corporation (Philadelphia, PA). These cigarettes are reported to produce sensory effects and taste similar to nicotine-containing brands of cigarettes. The availability of these cigarettes affords a unique opportunity to investigate the sensory and behavioral aspects of smoking, and to serve as a control condition in studies of the effects of nicotine *per se*. Although to date no studies have explored this issue, these cigarettes may have a role in the acute management of early smoking withdrawal symptoms (i.e., craving), when used in combination with nicotine replacement. Moreover, it is possible that sensory replacement strategies may prove useful for particular groups of smokers (e.g., highly dependent smokers).

Only a few studies have compared the effects of de-nicotinized or related types of cigarettes to commercially available cigarettes. Those studies that have been conducted, summarized in Table 1, have produced mixed results. Although the studies are consistent in demonstrating that cigarettes with little or no nicotine can produce smoking satisfaction and craving reduction, they vary in the degree to which the magnitude of these effects was comparable to those of nicotine-containing cigarettes. In an effort to explore a potential source of this variability, namely, individual differences, we conducted a pooled analysis of nine studies from our laboratory, in which the acute subjective effects of Next® cigarettes were compared to subjects' own brands. Acute subjective ratings of drugs have been shown repeatedly to be related to abuse potential (e.g., Fischman & Foltin, 1991), and these variables in particular are likely to relate to the maintenance of smoking.

The data set for the analysis was collected from 142 non-menthol smokers in nine studies, recruited from the Raleigh–Durham–Chapel Hill, NC, area. Each study had similar inclusion and exclusion criteria (e.g., minimum number of cigarettes per day of 15–20, minimum nicotine yield of at least 0.5 mg/cigarette, no medical or psychiatric illnesses) and used similar dependent measures to assess the effects of cigarettes. All of the studies included in the analyses were conducted with the Next® cigarette. Originally manufactured by Philip Morris, Inc., these cigarettes contain tobacco from which the nicotine has been selectively extracted by high-pressure carbon dioxide. They have a taste similar to nicotine-containing brands of cigarette, and the tar delivery, when smoked by FTC criteria, is 9 mg. However, the nicotine delivery is extremely low, less than 0.1 mg; therefore, these cigarettes produce sensory effects similar to those of nicotine-containing cigarettes without providing significant levels of nicotine. All studies were approved by the Duke and/or Veterans Affairs Medical Centers Institutional Review Boards, and informed consent was obtained from all subjects prior to participation.

Methods

The primary dependent measures explored in these analyses were smoking satisfaction and craving reduction obtained from smoking nicotine-containing as compared to de-nicotinized cigarettes. These variables were selected *a priori* as being most relevant to smoking-related reward. Data on satisfaction and craving reduction were gathered from two questionnaires, the Cigarette Evaluation Scale (CES; Westman, Levin, & Rose, 1992), and the Sensory Questionnaire (SQ), which were completed immediately after smoking a cigarette. The CES asks subjects to rate the extent to which the cigarette they just smoked was satisfying, tasted good, made them dizzy, calmed them down, helped them to concentrate, made them feel more awake, reduced appetite, made them nauseous, decreased irritability, produced enjoyable sensations in the throat and chest, and immediately reduced craving for cigarettes, on a Likert-type scale from not at all (1) to extremely (either 5 or 7, depending on study). For the purposes of this analysis, we used data from the last item on this questionnaire as a measure of craving reduction. For one study, data on craving were obtained from pre- to post-smoking changes in the craving subscale score from the

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Table 1. Effects of de-nicotinized tobacco cigarettes on ratings of liking and craving relative to nicotine-containing cigarettes

Author	Number of Subjects	Intent to quit	Mean number of cigarettes per day	Mean nicotine yield-usual brand	Design (within- or between-subjects)	Abstinence condition	Smoking pattern	Satisfaction vs. usual brand	Craving reduction vs. usual brand
Hasenfratz, Baldinger, & Battig (1993)	12	No	21.1	0.81	Within	a.m. prior to session	*Ad lib*	Lower	Lower
Rose *et al.* (1994)	12	Yes	28.0	0.91	Within	Overnight	Controlled	Similar	Similar
Baldinger, Hasenfratz, & Battig (1995)	12	No	24.3	Not available	Within	Not available	*Ad lib*	Lower	Lower
Butschky, Baily, Henningfield, & Pickworth (1995)	7	No	26.4	1.15	Within	12 hours	Controlled	Lower	Similar
Lane *et al.* (1995)	18	No	20.9	>0.70	Within	Overnight	*Ad lib*	Lower	Lower
Rose & Behm (1995)	20	Yes	26.8	0.98	Within	Overnight	*Ad lib*	Similar	Similar
Rose, Westman, & Behm (1996)	80	Yes	29.4	0.79	Between	Overnight	Controlled	Similar	Lower
Westman, Behm, & Rose (1996)	6	Yes	28.5	0.98	Within	Overnight	Controlled	Similar	Similar
Gross *et al.* (1997)	10	No	28.3	1.07	Within	Not abstinent	Controlled	Lower	Similar
Rose *et al.* (in progress)	13	Yes	29.4	0.79	Between	Overnight	*Ad lib*	Lower	Lower
Lane *et al.* (unpublished)	27	No	21.7	1.03	Within	Overnight	Controlled	Lower	Lower

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Shiffman–Jarvik questionnaire (Shiffman & Jarvik, 1976), because CES data were not available. The SQ asks subjects to rate how much they liked the cigarette they had just smoked and how much it satisfied them, how high in nicotine the cigarette appeared to be, and how similar the cigarette was to their own brand. In addition, the questionnaire presented subjects with a diagram of the respiratory tract and asked them to rate the strength of the cigarette puffs on their tongue, nose, back of mouth and throat, windpipe and chest, on a 1–7 Likert-type scale. For this analysis, we used the mean of the liking and satisfaction ratings as an overall measure of smoking satisfaction. For both questionnaires, data were calculated as difference scores (nicotine-containing minus de-nicotinized cigarette ratings), so that positive ratings indicated more satisfaction or craving reduction from the nicotine-containing cigarette, whereas neutral or negative ratings indicated no difference or higher ratings, respectively, from the de-nicotinized cigarette. Because the results of the separate analyses for craving reduction and smoking satisfaction suggested that these two measures were highly correlated, we calculated the mean of the two ratings and re-analyzed the data with this composite reward rating.

Data analyses were conducted using multiple regression with backward elimination. Five potential predictor variables were entered into the model: study, gender, race, years smoked, and total score on the Fagerström Test of Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; Kozlowski, Porter, Orleans, Pope, & Heatherton, 1994; Pomerleau, Carton, Lutzke, Flessland, & Pomerleau 1994; Tate and Schmitz 1993). Cigarettes per day and nicotine yield of preferred cigarette were not entered as predictor variables because these variables contribute to total FTND score, and would also be explored in subsequent analyses with individual FTND items (see below). Non-significant predictor variables were eliminated one at a time until only significant ($p \leq 0.05$) variables remained in the model. Because FTND score emerged as significant in most models, we conducted follow-up analyses to determine which individual FTND items were related to the composite reward score. The original analytic strategy was repeated with the individual items being entered and backward eliminated as described above.

The analyses conducted on nicotine-containing minus de-nicotinized cigarettes provides information on the relative ratings assigned to the two cigarette types, and gives an estimate of the relative importance of nicotine *per se* to smoking reward. However, these analyses do not address the possibility that individual differences in responses to the different cigarettes types reflect not positive responses to de-nicotinized cigarettes but rather blunted responses to nicotine as a result of tolerance. To address this issue, separate regression analyses were conducted on ratings of each cigarette type.

Results

Subject characteristics

Data from 142 subjects were included in the analysis. Fifty-eight per cent of the subjects were male, and 88% were Caucasian. Their mean age was 36.4 years old (SE = 0.93; range 18–65). Subjects smoked an average of 24.5 (SE = 0.70; range 10–60) cigarettes per day of a mean nicotine yield of 0.9 (SE = 0.02; range 0.5–1.7) mg when smoked by FTC criteria. They had smoked for an average of 19 years (SE = 0.92; range 1–48) at the time of participation in the study, and had average FTND scores of 5.5 (SE = 0.16; range 1–10).

Cigarette ratings

As a group, subjects reported substantial reward (i.e., the mean of craving reduction and smoking satisfaction ratings) from both nicotine-containing and de-nicotinized cigarettes, but, as expected, ratings were highest after smoking cigarettes containing nicotine [mean (SE) of 4.05 (0.15) for nicotine-containing-cigarettes vs. 3.36 (0.14) for de-nicotinized cigarettes; one-way ANOVA, $F(1,137) = 23.69$, $p = 0.0001$]. Interestingly, the final regression model indicates that there were significant individual differences in cigarette ratings, with some individuals assigning approximately equal ratings to the two kinds of cigarettes (see below), and others reporting greater reward from nicotine-containing cigarettes. Cigarette ratings are summarized in Table 2.

Regression model: NIC–DENIC

Of the five original potential predictors, including total FTND score, entered into the first model, only three predictors, FTND score, gender and study, remained significant in the final model. There were no significant effects of race or years smoked. The final model was as

Table 2. Mean (SE) cigarette ratings by gender and FTND score

Ratings	Males	Females	FTND<6	FTND≥6
DENIC	3.7 (0.2)	3.2 (0.2)	3.0 (0.2)	3.7 (0.2)
NIC	4.2 (0.2)	4.1 (0.2)	4.0 (0.2)	4.3 (0.2)
NIC-DENIC	0.5 (0.2)	0.9 (0.2)	1.0 (0.2)	0.4 (0.2)

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Table 3. Mean (SE) cigarette ratings by study

Study	DENIC	NIC	NIC-DENIC
Rose & Behm (1995)	3.8 (0.2)	4.3 (0.3)	0.5 (0.2)
Westman *et al.* (1996)	5.2 (0.6)	5.0 (0.5)	−0.2 (0.7)
Rose *et al.* (1994)[a]	1.5 (0.2)	1.7 (0.3)	0.2 (0.3)
Lane *et al.* (1995)	2.9 (0.4)	5.5 (0.4)	2.6 (0.5)
Lane *et al.* (unpublished)	3.4 (0.3)	4.7 (0.3)	1.3 (0.3)
Rose *et al.* (unpublished)	3.0 (0.3)	2.8 (0.3)	−0.1 (0.2)
Rose *et al.* (submitted)	4.3 (0.3)	4.5 (0.3)	0.2 (0.3)
Brauer, Behm, Westman, Patel, & Rose (1999)	4.5 (0.3)	4.6 (0.3)	0.1 (0.2)
Brauer *et al.* (in preparation)	2.6 (0.4)	3.9 (0.4)	1.3 (0.6)

[a] Cigarettes were rated on a scale of 1–5, rather than 1–7.

follows: FTND: $F(1,120) = 6.20$, $p = 0.014$, beta = −0.174; study: $F(8,120) = 6.40$, $p = 0.0001$; gender: $F(1,120) = 5.54$, $p = 0.020$, beta (male) = 0.00, beta (female) = 0.622; $r^2 = 0.345$. Several interesting findings emerged from this analysis. First and most interestingly, there was a significant negative correlation between the difference in ratings between nicotine-containing and de-nicotinized cigarettes (NIC–DENIC) and FTND scores, such that more highly dependent subjects assigned more similar ratings to the two cigarette types than less-dependent smokers, who obtained more reward from nicotine-containing cigarettes. When expressed as a median split, subjects with high dependence, defined as a total FTND score of ≥6, had an average NIC–DENIC difference of 0.42 (0.18), as compared to those with low to moderate dependence (FTND<6), who had a mean difference of 1.04 (0.24). Lower scores in the highly dependent group reflect more indifference to the two cigarette types, in that very similar ratings were assigned whether the cigarettes contained nicotine or not.

Second, cigarette ratings also tended to vary as a function of gender. On average, males were more indifferent to the effects of nicotine than females. The mean NIC–DENIC rating for males was 0.53 (0.18), whereas for females the mean rating was 0.93 (0.24). Thus, males assigned relatively less import to the psychopharmacological effects of nicotine than did females. Interestingly, there was no gender×FTND interaction for this measure.

The effects of study were difficult to characterize along a single dimension. Mean ratings for each cigarette type as a function of study are presented in Table 3.

Regression model: DENIC only

A separate regression analysis for DENIC ratings only suggests that the basis for this FTND effect is ratings of DENIC cigarettes, rather than diminished responses to nicotine. When the same backward elimination process was conducted for DENIC ratings, only FTND ($F(1,127) = 5.61$, $p = 0.019$, beta = 0.158) and study ($F(8,127) = 6.07$, $p = 0.0001$) emerged as significant predictors. Data from a mean split analysis demonstrate that, as expected, highly dependent subjects assigned de-nicotinized cigarettes a mean rating of 3.72 (0.20), as compared to less-dependent subjects, who assigned a mean rating of 2.98 (0.19).

When explored in the context of DENIC ratings only, there was no significant gender effect [mean for females = 3.16 (0.23) vs. mean for males = 3.67 (0.17)]. Nevertheless, the direction of the gender difference, with females liking de-nicotinized cigarettes less than males, is consistent with the results of the previous analysis.

Regression model: NIC only

Regressions for NIC ratings only support the notion that group differences in tolerance to the effects of nicotine does not account for our findings. Of the predictor variables entered into the regression, only study emerged as significant ($F(8,130) = 10.09$, $p = 0.001$; see Table 3).

Regression model with individual FTND items

Based on the obvious import of FTND scores to ratings of cigarette reward, we conducted an additional analysis to determine which individual FTND items most predicted significant reward from smoking-related sensory cues (i.e., de-nicotinized cigarettes). Using the regression approach described above, we examined the difference score (NIC–DENIC) with respect to the following FTND items [scoring]: (1) How long after waking do you smoke your first cigarette? [within 5 min = 3; 6–30 min = 2; 30–60 min = 1; greater than 60 min = 0]; (2) Do you find it difficult to refrain from smoking in places where it is forbidden? [yes = 1; no = 0]; (3) Which cigarette of the day would you most hate to give up? [first cigarette of the day = 1; all other cigarettes = 0]; (4) How many cigarettes do you smoke per day? [greater than 31 = 3; greater than 21 but les than 30 = 2; greater than 11 but less than 20 = 1]; (5) Do you smoke more in the morning than during the rest of the day? [yes = 1; no = 0]; (6) Do you smoke even when you are ill? [yes = 1; no = 0].

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NIC–DENIC

In the first analysis, of NIC–DENIC differences, two FTND items, Question 3 (which cigarette of the day would you most hate to give up; $F(1,132) = 5.99$, $p = 0.016$, beta = −0.721) and Question 4 (cigarettes/day; $F = 5.02$, $p = 0.027$; beta = −0.446) were significantly related to ratings of smoking reward ($r^2 = 0.068$). For Question 3, the mean rating for subjects who scored 1 (first cigarette of the day) was 0.46 (0.16), and the mean for those who scored 0 (all other cigarettes) was 1.09 (0.27), indicating that for subjects who most hated to give up the first cigarette of the day, ratings for the NIC and DENIC cigarettes were highly similar, whereas the remaining subject ratings for NIC cigarettes were significantly higher. To the extent that most missing the first cigarette of the day is considered an index of relatively higher dependence, these findings are consistent with the notion that more dependent subjects are more indifferent to nicotine-containing vs. de-nicotinized cigarettes than less dependent subjects.

A similar pattern emerged for Question 4 ratings. Ratings were nominalized in order to obtain mean values. Mean ratings in each category are as follows: score = 0 (smoke fewer than 11 cigarettes per day; $n = 4$), mean = −0.50 (0.35); score = 1 (smoke 11–19 cigarettes per day; $n = 58$), mean 1.09 (0.24); score = 2 ($n = 61$; smoke 21–30 cigarettes per day), mean = 0.60 (0.19); score = 3 (smoke greater than 31 cigarettes per day; $n = 15$), mean = −0.13 (0.40). Thus, with the exception of the small number of subjects who smoked fewer than 11 cigarettes per day, NIC–DENIC ratings were negatively correlated with cigarettes per day. Again, these findings are consistent with the notion that more highly dependent subjects place relatively less value on nicotine *per se* than do less dependent smokers.

DENIC only

A separate regression analysis with DENIC-only ratings yielded different results. In this analysis, only Question 1 (how soon after waking do you smoke your first cigarette?) was significantly related to cigarette ratings ($F = 5.78$, $p = 0.018$, $r^2 = 0.041$, beta = 0.378). Mean ratings were as follows: score = 0 (greater than 60 min), mean = 1.38 (0.18); score = 1 (30–60 min), mean = 3.21 (0.31); score = 2 (6–30 min), mean 3.64 (0.20); score = 3 (within 5 min), mean = 3.43 (0.25). These results indicate that subjects who smoked within 30 min of awakening were more likely to assign higher ratings of smoking reward than those who did not.

NIC only

No FTND items emerged as significant predictors of cigarette ratings.

Discussion

With each puff of cigarette smoke, smokers inhale over 4000 chemicals, each having potentially distinctive subjective effects. Given this fact, it is perhaps naive to expect that only the psychopharmacological effects of nicotine motivate smoking behavior. Indeed, the results of several previous studies confirm the critical role of smoking-related sensory cues. For example, we have shown that de-nicotinized cigarettes produce substantial craving reduction and smoking satisfaction (Rose & Behm, 1995). Interestingly, the results of this analysis indicate that the degree to which sensory factors maintain smoking may differ among smokers. Our analyses demonstrate a significant relationship between ratings of smoking reward and FTND scores, indicating that more dependent smokers rely more heavily on sensory cues than do less dependent smokers. In contrast, less dependent subjects appear to rely more heavily on the direct effects of nicotine.

The reasons why more dependent smokers might rate de-nicotinized and nicotine-containing cigarettes similarly may relate to the more prolonged and intensive associations of smoking-related sensory cues with the psychopharmacological effects of nicotine (see Rose & Levin, 1991). That is, with more prolonged and intensive pairing between the direct CNS effects of nicotine and the sensory effects of cigarette smoke, the ability of the sensory elements of smoke to induce conditioned reinforcing effects strengthens. If this were the case, then sensory effects of cigarette smoke, in their own right, would be rewarding. Alternatively, these results may reflect more extensive tolerance development to the effects of nicotine in heavier, more dependent smokers. That is, as the extent of acute or (perhaps) chronic tolerance to nicotine increases, the incremental effects of nicotine in cigarette smoke are less pronounced. As this occurs, the psychopharmacological effects of nicotine would likely become relatively less important in maintaining smoking. Although it is possible that the development of chronic tolerance contributes to the findings reported here, our analyses with DENIC ratings alone and NIC ratings alone clearly indicate that the secondary reinforcing effects of smoking-related sensory cues play a role in the maintenance of smoking in highly dependent smokers. The notion that conditioned reinforcers can contribute to drug-taking and/or withdrawal symptoms has been shown in previous studies with both animal and human subjects (e.g., Childress, McLellan, & O'Brien, 1986; O'Brien, Childress, McLellan, Ehrman, & Ternes, 1988; Stewart & Eikelboom, 1987). For example, O'Brien and colleagues have repeatedly shown that cues associated with the administration of opiates can increase drug craving (Childress *et al.*, 1986; O'Brien *et al.*, 1988). These findings underscore the complex nature of smoking and other drug use and emphasize the fact that substitution for or blockade of the central psychopharmacological effects of drugs may not be sufficient to reduce drug taking.

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Another interesting finding in this study relates to the gender differences observed in this study. On average, women had greater NIC–DENIC differences, and lower scores on ratings of de-nicotinized cigarettes alone. These results suggest that women assign more import to the direct psychopharmacological effects of nicotine than to the secondary reinforcing (i.e., sensory) effects, whereas men assign more equal relevance to nicotine and sensory cues. This pattern of results goes counter to those previously reported by Perkins and colleagues (e.g., 1992, 1996), who have shown in laboratory studies that women rate the sensory aspects of smoking as more salient than men. Perkins and others have used these results to suggest that perhaps nicotine replacement therapies are less effective for women because women rely less heavily on the psychopharmacological effects of nicotine than on other aspects of cigarette smoke. In contrast, our results suggest that perhaps nicotine is more salient to women, and that nicotine replacement therapies fail because there is insufficient nicotine replacement in this population. However, before we make this assertion with confidence, more prospective studies with de-nicotinized cigarettes should be conducted with respect to gender differences. The studies of Perkins and colleagues have primarily explored other routes of administering sensory impact (e.g., nicotine nasal spray and nicotine inhaler), which also deliver additional nicotine. Thus, the extent to which their findings would extend to smoking-related sensory cues is unclear.

The final models resulting from our analyses indicated that ratings also varied as a function of study. It is not clear why study was significant in our models, but several possibilities exist. First, it is possible that the studies varied with respect to motivation to quit smoking. Indeed, some of the studies included in the analysis were laboratory studies in which subjects were paid to participate and did not have to quit smoking, whereas others were smoking cessation trials. However, since subjects were not directly queried about their intentions to quit, it did not seem prudent to include this variable in the model. Second, the studies undoubtedly varied in terms of the context in which smoking took place. For example, in some studies subjects smoked through a controlled smoking apparatus, and in others they smoked *ad lib*. Third, the studies differed in terms of their purpose, and this may have influenced how smoking was measured or the importance of the cigarette rating data to the overall design. For instance, in one study, the antinociceptive effects of nicotine were of primary interest (Lane *et al.*, 1995), whereas others were specifically designed to compare cigarette types as was done in this analysis. Other, as yet undefined, differences between studies may also have contributed to our findings. Future studies should prospectively manipulate some of these parametric dimensions in an effort to characterize and systematize within-and between-subjects variability in response to de-nicotinized cigarettes.

The findings described in this paper have important implications, both for laboratory studies of smoking and for the development of effective smoking cessation strategies. One implication for laboratory studies is that the role of sensory and motor components of smoking cannot be ignored, and should be rigorously controlled with de-nicotinized cigarettes or similar technology. For instance, studies attempting to explore nicotine regulation by providing smoking preloads, or studies assessing nicotine preference using cigarettes, need to consider carefully the possible influence of sensorimotor factors in their data. For example, Behm and Rose (1994) have shown that capsaicin-enhanced low tar and nicotine cigarettes substantially reduce craving for cigarettes by mimicking respiratory tract cues associated with cigarette smoking.

Another finding that may have relevance for future studies is the fact that ratings of craving reduction and smoking satisfaction seem to co-vary – indeed, this is the reason that we elected to use a composite reward variable in the present analyses. A regression analysis of satisfaction vs. craving reduction ratings showed a very strong correlation between these factors ($r = 0.53$). A similar relationship has been shown in a previous paper (Behm & Rose, 1994). The fact that these cigarette ratings co-vary supports the idea that smokers may smoke to relieve withdrawal symptoms, rather than merely for enjoyment. That is, it is possible that smoking satisfaction is derived largely from craving reduction, and that the measures explored in these studies are one and the same. However, it is likely that craving reduction and smoking satisfaction represent separate constructs; it is possible to reduce craving with manipulations that do not impact upon satisfaction (e.g., nausea).

The findings described here also suggest that future laboratory studies need to explore the basis for compensatory increases or decreases in smoking following alterations in the nicotine or tar content of cigarettes. To date, no studies have systematically explored this question by allowing subjects to smoke de-nicotinized tobacco (as opposed to herbal or lettuce) cigarettes over a prolonged period of time. A study to examine this issue is currently underway. Although the prevailing opinion is that smokers alter smoking topography based on changes in nicotine delivery, the data described here suggest that subjects may also attempt to regulate, to some extent, the sensory impact or quality experienced. Nicotine itself is a local irritant, and in addition stimulates nicotine receptors in the respiratory tract, and thus nicotine dose is related to the intensity of airway sensations (Herskovic, Rose, & Jarvik, 1986; Rose & Hickman, 1988). However, tar also plays a role in sensory impact by modulating the sensory effects of nicotine, and contributes to the taste, aroma, and airways sensations of smoking. Therefore, smokers may seek a particular ratio of nicotine to tar, as reflected in the intensity and quality of sensory cues. Studies exploring pharmacological or behavioral manipulations that decrease craving in the laboratory may be useful in developing strategies for alleviating craving for cigarettes that occurs during smoking cessation attempts.

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The small number of published studies exploring the role of sensory factors in smoking underscores the need for more laboratory research into sensory effects of smoking. Many questions remain unanswered, despite their importance to theories of smoking reward in general and to smoking cessation efforts. For instance, the mechanism by which these cigarettes reduce craving should be explored. In addition, attempts should be made to replicate the findings of currently published studies with a variety of different procedures, dependent measures, and populations. It also remains to be determined whether brand loyalty may underlie lower ratings of satisfaction of de-nicotinized cigarettes in some individuals. Finally, future laboratory studies should attempt to replicate the relationship between level of tobacco dependence and importance of sensory aspects of smoking. In particular, it will be important to determine whether the responses after a single cigarette, as assessed in this analysis, would persist over a larger number of cigarettes. The fact that Next® and similar products have not fared well in the marketplace suggests that the effect reported here may be short-lived.

The findings of this analysis also provide useful insight into aspects of smoking that should be taken into account in smoking cessation strategies. The fact that sensory factors play an important role in smoking helps to explain the lack of more robust effects of nicotine replacement therapies for smoking cessation. Transdermal or buccal administration of nicotine may provide many of the central effects of nicotine that smokers seek, and may also reduce some of the cognitive, subjective and physiological symptoms of cigarette withdrawal; however, these routes of administration do not produce the important airway sensations smokers seek. Although de-nicotinized cigarettes do not exactly reproduce the airway sensations of commercially available cigarettes, they produce substantial smoking satisfaction and craving reduction, and may enhance the withdrawal relief provided by nicotine replacement. Although it would be counterproductive to suggest that smokers switch to these cigarettes for a prolonged period of time, it may be fruitful to provide a limited number of these cigarettes to smokers during cessation attempts, for use in conjunction with nicotine replacement therapy. This strategy may be particularly effective during early abstinence, and in highly dependent smokers. By using this strategy, smokers could be weaned from the pharmacological effects of nicotine with the expectation that the conditioned rewarding effects of airway stimulation would subsequently extinguish. Alternatively, other forms of nicotine replacement, such as the nicotine inhaler, which include a sensory component, may be useful.

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